REMARKS

This Preliminary Amendment is submitted to resolve some of the issues raised in the Advisory Action dated February 11, 2002. Specifically, the Examiner recommended that claims 50 and 51 be amended to recite genes *encoding* the proteins recited in the Markush groups recited in these claims. She also recommended that the phrase "developmental genes" in claim 51 be amended to read "genes controlling development of an organism" to maintain antecedent basis with claim 15. Applicants have adopted the Examiner's suggestions by way of amendment above. Applicants further note that those of skill in the art would immediately know whether any given protein was a "metabolic enzyme" or a "growth/differentiation factor or receptor" because such proteins have been well characterized. Therefore the metes and bounds of the claim with regard to these terms would be clear to those of skill in the art.

According to Part B of the attachment to the Advisory Action, starting on page 3, the Examiner agrees that the experiments reported in the Neuron paper used the same FLP recombinase version and the same methodology as that disclosed in the specification. However, the Examiner does not believe that the claims fairly reflect what the specification or the Neuron paper describes. For instance, while the examiner concedes that the specification teaches how to use mice that have a FLP recombinase transgene under control of a tissue specific promoter and a reporter gene under control of a ubiquitous promoter wherein the reporter gene comprises a disruption of two FLP-recognition sequences in direct repeat orientation such that the reporter gene produces active product only when in the recombined form (for instance, in the utility of cell fate mapping), she does not concede that the specification teaches how to use all other arrangements of FLP recombinase and recognition sequences as encompassed by the claim. The examiner seems particularly

concerned that the claims read on creating a mouse with a null phenotype as a result of FLP-mediated recombination, because this would require recombination in every cell of the mouse, an event that the specification allegedly fails to enable.

Applicants respectfully disagree with the Examiner's position because the claims specify that recombination occurs in *a cell* expressing sufficient recombinase activity, not in every cell of the mouse. Further, the scope conceded by the examiner is unduly narrow in that the specification teaches how to detect recombination using other means than a reporter gene, and also teaches other uses for the FLP recombinase that would not require the specific combination of promoters mentioned by the examiner. Furthermore, the specification teaches using FLP sequences in inverted repeat orientation, for instance to cause inversion of an intervening sequence or gene. See pages 4-5 of specification.

In any case, no further disclosure is required to enable the use of the FLP recombinase system for any given purpose. Indeed, the means to express the recombinase in any desired cell is provided by coupling expression of FLP to an appropriate promoter. Once expression is achieved, the recombinase automatically facilitates recombination at the FLP sites. The recombinase does not discriminate once it is expressed, therefore, it is unclear to applicants why the examiner would require exemplification of the system for all uses encompassed by the claims.

Nevertheless, applicants have added new claims 52-65, which applicants believe are more clearly directed to uses such as the cell fate mapping embodiment. For instance, claim 52 is directed to a transgenic mouse comprising an Flp transgene integrated into the genome of the transgenic mouse, wherein the Flp transgene is expressed from a tissue specific or a developmental stage specific promoter in at least one cell of the transgenic mouse at a level sufficient to catalyze recombination

between two FLP-recognition sequences in direct repeat orientation in said cell.

Support for such a claim may be found in original claim 20, which allows for regulation of FLP recombinase activity according to developmental stage or tissue type, and would therefore cover the use of a promoter that is expressed during development of a particular tissue, but not necessarily in the developed tissue itself (as might be encountered in cell fate mapping).

Claim 53 is directed to the transgenic mouse of claim 52, wherein said recombination between said two FLP recognition sequences is detected by activation of a gene, wherein said gene produces a detectable product only when in recombined form. Support for this claim may be found at the very least at page 36, first full paragraph of the specification.

New claim 54 further specifies that the gene producing a detectable product is expressed from a ubiquitous promoter in said at least one cell expressing a sufficient level of said Flp transgene. Support for this claim may be found at the very least at page 37, first full paragraph.

New claim 55 further defines the detectable product as being one of the histochemical markers disclosed at pages 20-21 of the specification (in the bridging paragraph).

New claim 56 further provides that the detectable product is a transcript expressed from said gene in recombined form that is detectable by *in situ* hybridization, as provided on page 20 of specification, last paragraph.

New claim 57 provides that the detectable product is a peptide tag encoded by said gene that is detectable by binding to a cognate binder, as provided on page 21 of specification, first paragraph.

New claim 58 further specifies that the peptide tag and cognate binder pair are selected from the group consisting of avidin-biotin, GST-glutathione, polyHis-divalent metal, MBP-maltose, 9E10 Myc epitope-antibody, protein A/G-immunoglobulin and SV40 T antigen-antibody, as also provided on page 21 of specification.

New claim 59 is specifically directed to a method of mapping the developmental fate of a cell *in vivo* comprising(a) providing a transgenic mouse comprising a genome which contains a Flp transgene under control of a tissue-specific or developmental stage specific promoter and at least two FLP recognition sequences in direct orientation; (b) expressing the Flp transgene at a level sufficient to catalyze site-specific recombination between said FLP recognition sequences in at least one cell; and (c) detecting said recombination in said at least one cell, wherein said recombination is evidence of expression of said Flp transgene in said cell or a developmental precursor to said cell. Support for this claim may be found at the very least at page 5, in the second and third full paragraphs.

New claims 60-65 are similar to new claims 53-58, support for which is discussed above.

No new matter has been added by any of the amended or newly added claims. Examination on the merits is respectfully requested.

Applicants respectfully submit that no new prohibited matter has been introduced by this Preliminary Amendment. Substantive examination of the amended claims is respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page is captioned APPENDIX.

Except for issues payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **constructive petition for extension of time** in accordance with 37 C.F.R. 1.136(a)(3).

Respectfully submitted
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APPENDIX

The following amendments were submitted above:

50. (Amended) The transgenic mouse according to claim 12, wherein transcription of said another transgene is controlled by a regulatory region selected from the group consisting of regulatory regions from the genes encoding β-actin, phosphoglycerate kinase, HMG-CoA reductase, major histocompatibility complex class I, β2-microglobulin, HSV thymidine kinase, Rous Sarcoma Virus regulatory elements, CMV intermediate early gene, and SV40 origin.

51. (Amended) The transgenic mouse according to claim 15, wherein said [developmental] genes controlling differentiation of a cell or development of an organism are selected from the group consisting of genes encoding adhesion molecules, cyclin kinase inhibitors, Wnt family members, Pax family members, Winged helix family members, Hox family members, cytokines, interleukins, growth/differentiation factors and their receptors, kinases, phosphatases, metabolic enzymes, and antigen receptors.